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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/991,721	MCCART ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15,17,18,25 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,15,17,18,25 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 28 February 2005 has been entered.

Claims 1-13, 15, 17, 18, 25 and 27-44 were pending and considered in the Final Office Action mailed 26 November 2004. Claim 1 was amended and claims 28-44 were canceled in the 28 February Paper. Claims 1-13, 15, 17, 18, 25 and 27 are presently pending and under consideration.

Response to Amendment

Rejection of claims 28-42 is rendered moot by the cancellation thereof.

Claim Rejections - 35 USC § 112

Rejection of claims 1-13, 15, 17, 18 and 27 under 35 U.S.C. 112, first paragraph, as containing new matter is withdrawn in view of the amendment of claim 1 such that it no longer recites "tyrosine kinase".

New Grounds

Claim construction

Claim 1 recites that the vaccinia virus expression vector comprised within the tumor cell is "comprised of a mutation in a thymidine kinase (TK) gene...and comprised of a mutation in at least one vaccinia virus growth factor (VVGF) gene". According to common English, the phrase "comprised of" is understood as "make up" or "constitute". Thus, the claim reads as though the mutation in a thymidine kinase gene and the mutation in at least one VVGF gene constitutes the entirety of the vaccinia virus expression vector. However, as the Office reads all transitional phrases other than "consisting of" as open, the phrase "comprised of" is read as "comprising". Therefore, the claim is understood to be directed to a tumor cell comprising a vaccinia virus expression vector, wherein said expression vector comprises a mutation in a thymidine kinase (TK) gene of the genome of said vaccinia virus to produce a negative TK phenotype and comprises a mutation in at least one vaccinia virus growth factor (VVGF) gene of the genome of said vaccinia virus to produce a negative VVGF phenotype, wherein said tumor cell is present *in vivo* in a mammal. In the interest of clarity, applicant is urged to amend the claim such that the literal recitation is consistent with this meaning.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-12, 15, 17, 25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mastrangelo *et al.* (1995) WO 95/31105 in view of Dorner *et al.* U.S. Patent No. 6,103,244 and in view of Buller *et al.* (1988) *J. Virol.* 62:866-874 (previously made of record).

As described above, the claims are understood to be directed to a tumor cell comprising a vaccinia virus expression vector, wherein said expression vector comprises a mutation in a thymidine kinase (TK) gene of the genome of said vaccinia virus to produce a negative TK phenotype and comprises a mutation in at least one vaccinia virus growth factor (VVGF) gene of the genome of said vaccinia virus to produce a negative VVGF phenotype, wherein said tumor cell is present *in vivo* in a mammal.

Mastrangelo *et al.* teaches a method comprising inducing expression of immune active cytokines in tumors *in situ* by delivering genes encoding said immune active cytokines into cells of a tumor in an animal using a vaccinia virus vector, wherein the tumor is in mammal and most preferably a human (see especially page 3, lines 28-3; the paragraph bridging pages 4-5; page 8, lines 12-36; and Example 7, beginning on page 13). The product made by the method of Mastrangelo *et al.* is a tumor cell comprising a vaccinia virus expression vector. Mastrangelo *et al.* fails to teach a vaccinia virus vector comprising a mutation in a TK gene to produce a negative TK phenotype and a mutation in at least one VVGF gene to produce a negative VVGF phenotype.

Dorner *et al.* teaches a vaccinia virus vector comprising a mutation in a TK gene to produce a negative TK phenotype (see especially Figures 4.1A and 4.2 and the caption thereto; see also the second and third full paragraphs in column 30 and the third full paragraph in column 9). Although Dorner *et al.* does not explicitly teach a vaccinia virus vector comprising a mutation in both the TK and VVGF genes, Dorner *et al.* does teach that safety is a major concern with the use of vaccinia virus as an immunizing agent and cites the work of Buller *et al.* as teaching attenuation of vaccinia virus to produce a less virulent strain by mutation of the viral growth factor gene (see especially the paragraph bridging columns 3-4).

Buller *et al.* teaches that deletion of the sequence encoding the EGF receptor-binding site of the VVGF gene resulted in an attenuated phenotype (see especially Figure 1, the caption thereto and Table 3). Buller *et al.* further teaches that the VGF^- mutation may be a desirable attenuation marker for inclusion in vaccinia virus recombinant vaccine strains such as the

vaccine vector described by Dorner *et al.* and the vaccine vector delivered into tumor cells in an animal according to the method of Mastrangelo *et al.*

The teachings of Mastrangelo *et al.*, Dorner *et al.* and Buller *et al.*, demonstrate that the use of vaccinia virus vectors to deliver nucleic acids into tumor cells, and vaccinia virus vectors comprising mutations in a TK gene to produce a negative TK phenotype and comprising a mutation in at least one VVGF gene to produce a negative VVGF phenotype were known to the skilled artisan at the time the instant invention was made.

Furthermore, it would have been obvious to the skilled artisan at the time the invention was made to combine the elements described in Mastrangelo *et al.*, Dorner *et al.* and Buller *et al.* according to the claims of the instant application. One would be motivated to combine these teachings based on the nature of the problem to be solved by the teachings of Mastrangelo *et al.*, which is to deliver immune active cytokines into tumor cells by means of a vaccinia virus vector, statements made in Dorner *et al.* indicating that the vector disclosed therein is particularly advantageous because it enables direct cloning of genes into the vector (see especially the second full paragraph in column 17), the teachings of Dorner *et al.* indicating that it is desirable to use vector strains comprising mutations of genes that result in decreased virulence (*Id.*) and the teaching of Buller *et al.* that the VGF^- mutation might be a desirable attenuation marker for inclusion in vaccine vectors (*Id.*).

Furthermore, Dorner *et al.* demonstrates that the TK^- vector described therein is an efficacious delivery vehicle and Buller *et al.* found that deletion of the VVGF gene, in spite of its effect of reducing virulence of the virus *in vivo*, did not affect virus replication under optimal cell growth conditions *in vitro* (see especially the paragraph bridging pages 871-872). Thus, one

would have a reasonable expectation of success in combining the TK$^-$ and VVGF$^-$ phenotypes in a single vector for use in the method of Mastrangelo *et al.* to produce the tumor cell of the instant claims.

For these reasons, the tumor cell of claim 1, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Furthermore, as the tumor cell of claim 25 is a product-by-process, wherein the product of Mastrangelo *et al.* in view of Dorner *et al.* and Buller *et al.* comprises all of the limitations of the product, the teachings of the art also render obvious the product of claim 25.

In addition, the limitations of the claims depending from claim 1 would also be obvious to one of ordinary skill in the art based on the teachings of Mastrangelo *et al.* in view of Dorner *et al.* and Buller *et al.* First, Mastrangelo *et al.* teaches that the vector should comprise an exogenous nucleic acid sequence according to claim 2, wherein the exogenous nucleotide sequence is a cytokine encoding gene according to claim 12 (see especially the first full paragraph on page 6).

Dorner *et al.* teaches a mutation comprising replacement of the viral TK gene with a multiple cloning site (see especially Figure 4.2 and the caption thereto). Thus, the limitations of claims 3-6, which require that the negative thymidine kinase phenotype results from a deletion of a TK gene sequence and an insertion or substitution of a nucleic acid sequence, would also be obvious in view of the art. Likewise, Buller *et al.* teaches a mutation comprising substitution of the EGF receptor binding site of the VVGF gene with the *E. coli lacZ* gene and renders obvious the limitations of the claims 7-11 (see especially Figure 1 and the caption thereto), which require that the negative VVGF phenotype results from a VVGF gene containing a deletion or

substitution mutation which might include deletion of the EGF-receptor binding site, as well as the limitations of claim 17, which requires that an *E. coli lacZ* gene is inserted into the VVGF site.

Furthermore, in the second full paragraph in column 23, Dorner *et al.* teaches that the vectors disclosed therein are produced by a virus particle containing a virus genome wherein expression of the genome produces a vaccinia virus according to claim 15 and in the caption of Figures 4.1 an 4.2, Dorner *et al.* teaches that the vectors can be constructed from the WR strain according to claim 27.

For these reasons, the tumor cell of claims 1-12, 15, 17, 25 and 27, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as obvious over the art.

Claims 1 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mastrangelo *et al.* in view of Dorner *et al.* and in view of Buller *et al.* as applied to claim 1 above, and further in view of Zhang *et al.* (1996) *Biochem. Biophys. Res. Commun.* 227:707-711.

As described above, the limitations of claim 1, as a whole, would have been obvious to one of ordinary skill in the art based on the teachings of Mastrangelo *et al.* in view of Dorner *et al.* and in view of Buller *et al.* Claim 18 further limits the vaccinia virus expression vector to comprising an enhanced GFP gene inserted into the VVGF site, which limitation is not disclosed in the teaching of Mastrangelo *et al.*, Dorner *et al.* or Buller *et al.* However, as described above, Buller *et al.* teaches insertion of the *E. coli LacZ* gene into the VVGF site as a marker for virus

comprising the mutation. Zhang *et al.* discloses a nucleic acid encoding an EGFP and teaches that it can be used as a marker gene (see throughout).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the EGFP marker gene of Zhang *et al.* for the *LacZ* gene of Buller *et al.* according to the limitations of the instant claim 18. Motivation to combine these teachings is found in Zhang *et al.*, which teaches that the EGFP reporter gene has a number of advantages over reporter genes such as *LacZ* (see especially the paragraph bridging pages 707-708, the first full paragraph on page 708 and the first full paragraph on page 711). Furthermore, one would have a reasonable expectation of success in combining these teachings because the use of GFP as a marker gene is a well-established technology.

For these reasons, the invention of claims 1 and 18, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a).

Claims 1, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mastrangelo *et al.* in view of Dorner *et al.* and in view of Buller *et al.* as applied to claims 1 and 12 above and further in view of Paoletti U.S. Patent No. 5,942,235.

As described above, the limitations of claims 1 and 12, as a whole, would have been obvious to one of ordinary skill in the art based on the teachings of Mastrangelo *et al.* in view of Dorner *et al.* and in view of Buller *et al.* Claim 13 limits the tumor suppressor gene of claim 12 to a p53 gene. Neither Mastrangelo *et al.*, Dorner *et al.* nor Buller *et al.* teach the tumor cell comprising a vaccinia virus vector comprising a tumor suppressor gene.

Paoletti, like Mastrangelo *et al.*, teaches cancer therapy using recombinant vaccinia virus vectors to elicit immune responses against tumor cells (see especially the abstract, the fourth full paragraph in column 6 and the paragraph bridging column 6-7). Paoletti further teaches that the inclusion of tumor associated antigens and administration directly into a tumor can elicit anti-tumor immune responses more rapidly and to sufficient levels to impede or halt tumor spread and potentially eliminate the tumor burden (third full paragraph in column 13 and the second full paragraph in column 14). In that same paragraph, Paoletti goes on to identify p53 as among the tumor associated antigens known to be of immunotherapeutic value in the treatment of tumors.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Mastrangelo *et al.* in view of Dorner *et al.* and in view of Buller *et al.* to include the tumor specific antigen p53 according to the teachings of Paoletti. Motivation to combine these teachings comes from the nature of the problem to be solved by the teachings of Mastrangelo *et al.*, which is to treat tumors by eliciting an immune response, and from the teachings of Paoletti, which indicate that inclusion of tumor associated antigens such as p53 can elicit anti-tumor immune responses more rapidly and to sufficient level to impede or halt tumor spread and potentially eliminate tumor burden (*Id.*). Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings in view of the teaching of Paoletti that p53 is among the tumor associated antigens known to be of immunotherapeutic value in treatment of tumors.

For these reasons, the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as unpatentable over the art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER